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EXAMINER	
CORDERO GARCIA, MARCELA M	
ART UNIT	PAPER NUMBER
1654	
MAIL DATE	DELIVERY MODE
09/16/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/564,324	RAJADHYAKSHA ET AL.	
	Examiner	Art Unit	
	MARCELA M. CORDERO GARCIA	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 May 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10,12-14,16 and 17* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10, 12-14, 16 and 17* is/are rejected.

7)☒ Claim(s) *1-10,12-14,16 and 17* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

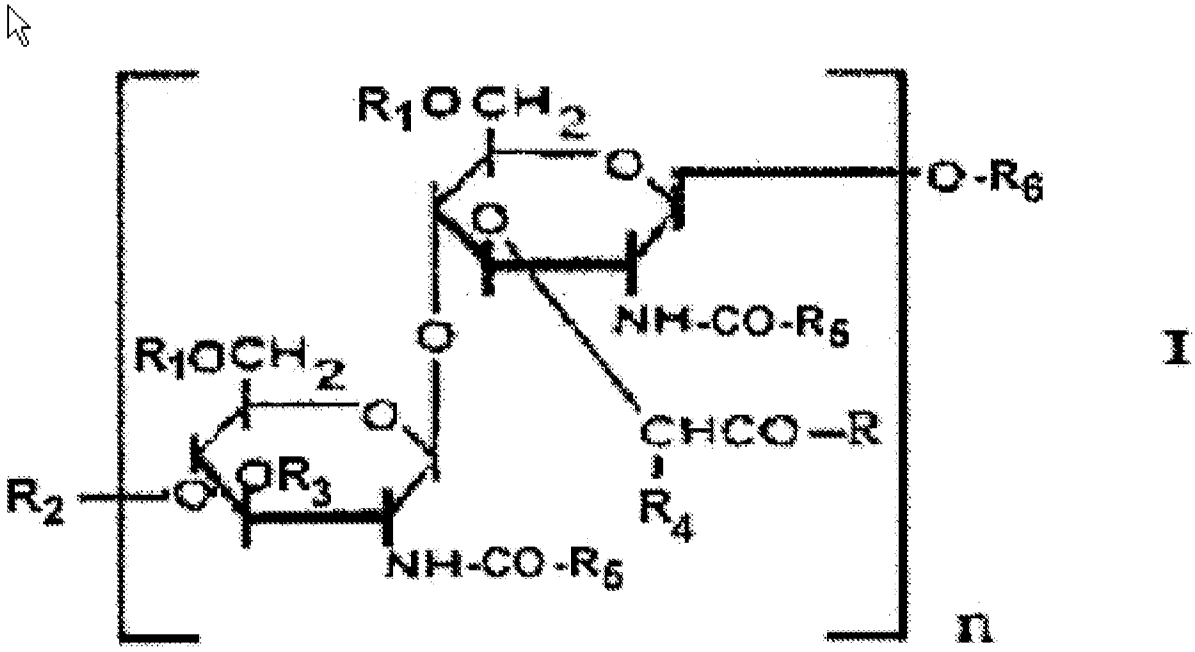
Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *01/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election without traverse of the species of formula I



I

wherein R_1 is H, R_2 is H, R_3 is H, R_4 is alkyl, R_5 is alkyl, R_6 is H, R is a linear peptide of from 2 to 6 amino acid residues and n is 1 (Step A) and of a flavone, derivatives, prodrugs or congeners thereof (Step B) in the reply filed on 12 May 2008 is acknowledged.

Status of the claims

Examiner thanks Applicants for pointing out that the pending claims are 1-10, 12-14 and new claims 16-17. Claims 1-10, 12-14 and 16-17 read upon the elected species. Claims 1-10, 12-14 and 16-17 are presented for examination on the merits.

Claim Objections

Claims 1-10, 12-14 and 16-17 are objected to because of the following informalities: It appears that there is a typographical error in claim 1, line defining the substituent R_5 which contains the phrase "C_6 or **$C_{,0}$** aryl group". Appropriate correction is required. All other claims that depend directly or indirectly from rejected claims and are, therefore, also objected for the reasons set forth above.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The MPEP states that the purpose of the written description requirement is to ensure that the inventor had possession, as of the filing date of the application, of the specific subject matter later claimed by him. The courts have stated:

> "To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); In re Gosteli, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) (" [T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." Lockwood, 107 F.3d at 1572, 41 USPQ2d at 1966." Regents of the University of California v. Eli Lilly & Co., 43 USPQ2d 1398.

The MPEP lists factors that can be used to determine if sufficient evidence of possession has been furnished in the disclosure of the Application. These include "level of skill and knowledge in the art, partial structure, physical and/or chemical properties,

functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention. Disclosure of any combination of such identifying characteristics that distinguish the claimed invention from other materials and would lead one of skill in the art to the conclusion that the applicant was in possession of the claimed species is sufficient." MPEP 2163.

Further, for a broad generic claim, the specification must provide adequate written description to identify the genus of the claim. In Regents of the University of California v. Eli Lilly & Co., the court stated:

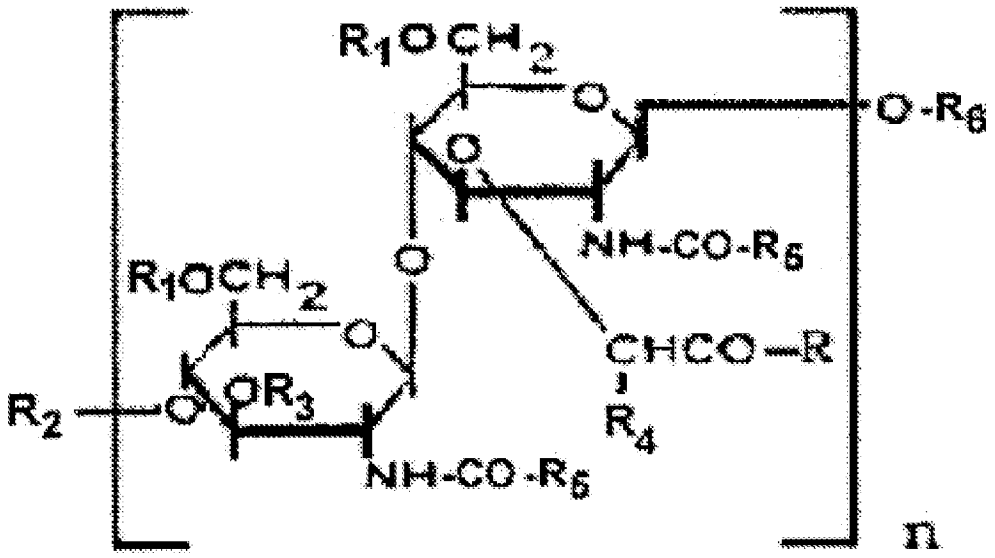
> "A written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials. Fiers, 984 F.2d at 1171, 25 USPQ2d at 1606; In re Smythe, 480 F.2d 1376, 1383, 178 USPQ 279, 284-85 (CCPA 1973) ("In other cases, particularly but not necessarily, chemical cases, where there is unpredictability in performance of certain species or subcombinations other than those specifically enumerated, one skilled in the art may be found not to have been placed in possession of a genus. . . ."). Regents of the University of California v. Eli Lilly & Co., 43 USPQ2d 1398.

The MPEP further states that if a biomolecule is described only by a functional characteristic, without any disclosed correlation between function and structure of the sequence, it is "not sufficient characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence." MPEP 2163. The MPEP does state that for generic claim the genus can be adequately described if the disclosure presents a sufficient number of representative species that encompass the genus. MPEP 2163. If the genus has a substantial variance, the disclosure must describe a sufficient variety of species to reflect the variation within that genus. See MPEP 2163. Although the MPEP does not define what constitute a sufficient number of

representative, the Courts have indicated what do not constitute a representative number species to adequately describe a broad generic. In Gostelli, the Court determined that the disclosure of two chemical compounds within a subgenus did not describe that subgenus. In re Gostelli, 872 F.2d at 1012, 10 USPQ2d at 1618.

In the instant case, the claims are drawn to methods for treating a metabolic or autoimmune disorder in a human or veterinary patient, said methodcomprising the steps of:

(A) administering to the patient a therapeutically effective amount of a compound having the formula



I

wherein:

R_1, R_2, R_3 each represents a hydrogen atom or a C_1-C_{22} acyl group;

R_4 represents a hydrogen atom or a C_1-C_6 alkyl group;

R5 represents a C_1-C_{21} alkyl group or a C_6 or $C_{,0}$ aryl group;

R_6 represents a hydrogen atom; and

R represents the residue of an amino acid or a linear peptide of up to from 2 to 6 amino acid residues. Furthermore, at least one of the residues may be optionally substituted with a lipophilic group through an ester or an amide bond; and n is 1 and 2; and

(B) administering to the patient a natural or synthetic compound that comprises a flavone, flavonoid, isoflavone or a derivative, prodrug or congener thereof.

. With regards to the phrase: "metabolic and/or autoimmune disease", the disclosure teaches that this phrase includes, but is not limited to, Amyotrophic Lateral Sclerosis (ALS), Multiple Sclerosis (MS), Type I Diabetes, Rheumatoid Arthritis, Psoriasis, etc. (e.g., page 10, lines 20-25). However, the terms autoimmune disease and metabolic disease are very broad generic terms drawn to any autoimmune and any metabolic disease, which are not adequately described and/or represented in the examples. The specification does provide examples of what qualify as methods of the claimed invention (see, e.g, disclosure, pages 31-35), however, these are limited to a few examples drawn exclusively to ALS treatment: Example 1 is drawn to a 39-year old male with bulbar onset ALS and the treatment consisted of luteolin, rutin and GMDP. Example 2 is drawn to a 50 year-old male with rapidly progressing bulbar onset ALS treated with luteolin, rutin and GMDP and GMDP-A. Example 3 is drawn to a 50 year-old male diagnosed with lower limb onset ALS treated with letolin, rutin and GMDP and GMDP-A. Example 4 is drawn to a 51 year-old diagnosed with upper limb onset ALS treated with luteolin and rutin, GMDP-A. Example 5 is drawn to a 57 year-old female ALS patient treated with lutolin, rutin and GMDP-A. Example 6 is drawn to a 45 year-old female with multiple limb and bulbar ALS treated with luteolin and rutin, GMDP-A. Example 7 is drawn to 25 ALS patients given intranasal GMDP-A for 1-4 months.

Please note that the instant examples are exclusively to treatment of ALS with GMDP and GMDP-A. As stated earlier, the MPEP states that written description for a genus can be achieved by a representative number of species within a broad generic. It is unquestionable claim 1 is a broad generic with respect all possible methods of treating autoimmune and metabolic diseases with the compounds encompassed by the claims. The possible structural variations are given by the R substituents, especially the peptidic substituents, which can have any sequence of residues therein, including optionally substituted with lipophilic groups, and include many other compounds beyond those disclosed as preferred embodiments (pages 16-21). It must not be forgotten that the MPEP states that if a biomolecule is described only by a functional characteristic, without any disclosed correlation between function and structure of the sequence, it is "not sufficient characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence." MPEP 2163. Here, though the claims may recite some functional characteristics, the claims lack written description because there is no disclosure of a correlation between function and structure of the compounds beyond compounds disclosed in the examples in the specification. Moreover, the specification lack sufficient variety of species to reflect this variance in the genus since the specification does not provide any examples of the method for other autoimmune diseases or metabolic diseases beyond ALS with the many possible compounds encompassed by formula I. The description requirement of the patent statute requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See In re Wilder, 736 F.2d 1516, 1521, 222 USPQ 369, 372-73 (Fed. Cir. 1984) (affirming rejection because the specification does "little more than outlin[e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate."). Accordingly, it is deemed that the specification

fails to provide adequate written description for the genus of the claims and does not reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the entire scope of the claimed invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

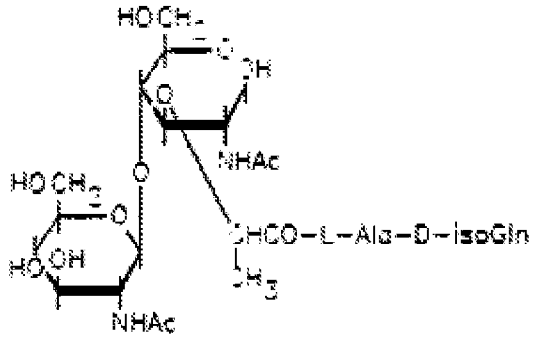
> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-6, 12-14 and 16-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ledger (WO 96/01645, cited in the IDS sated 1/10/06) in view of Lazendörfer et al. (US 5,952,373).

Ledger teaches a method for treating psoriasis, which reads upon an autoimmune and/or metabolic disorder (e.g., page 1, lines 7-22; page 24, lines 1-10), in a human or veterinary patient, said method comprising the steps of:

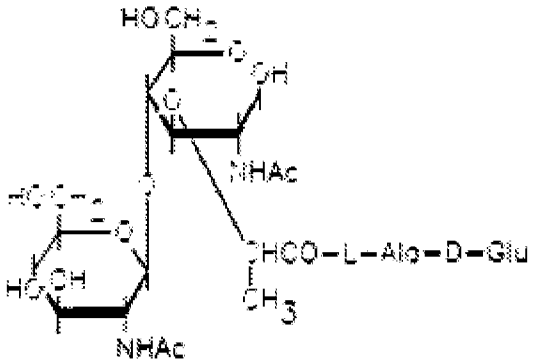
(A) administering to the patient a therapeutically effective amount of a compound having the formula (see pages 9-10):



GMDP

wherein R_1 is H, R_2 is H, R_3 is H, R_4 is alkyl (CH_3), R_5 is alkyl (CH_3), R_6 is H, R is a linear peptide of from 2 to 6 amino acid residues (L-Ala-D-isoGln) and n is 1.

and/or



GMDP-A

wherein R_1 is H, R_2 is H, R_3 is H, R_4 is alkyl (CH_3), R_5 is alkyl (CH_3), R_6 is H, R is a linear peptide of from 2 to 6 amino acid residues (L-Ala-D-Glu) and n is 1.

Ledger teaches that muramyl peptides “GMDP” (as in the limitations of instant claims 2, 4-5) and “GMDP-A” (as in the limitations of instant claims 3-5) may be used

either singly or in combination with each other in the invention (as in the limitation of instant claim 4: “administering GMDP and GMDP-A”). Legder teaches topical (e,.g., page 25, lines 13-24). Ledger also teaches oral administration of the compounds (e.g., page 24, lines 10-34) which reads upon the limitation of claim 6: “administered enterally”. Additionally, Ledger teaches that muramyl peptide compounds may be used in combination with other compounds, whether formulated together or separately; for example, a muramyl peptide compound may be administered orally and another compound administered topically. When used in combination, either with each other or with other compounds, administration can be simultaneous, separate or sequential (e.g., page 25, lines 25-33) which read upon the limitations of claim 5: “comprising administering GMDP and GMDP-A in separate doses at separate times“, claim 12 “wherein Step A and Step B are carried out substantially simultaneously”; claim 13: “wherein Step A and Step B are carried out at different times" and the limitation of claim 14: “wherein the compound of Step A and the compound of Step B are administered in a fixed dosage combination pharmaceutical preparation (e.g., orally administered tablet, e.g., page 24, lines 10-34; page 25, lines 31-33).

Ledger does not expressly teach the limitation of claim 1: “administration of a flavone, flavonoid, isoflavone or a derivative, prodrug or congener thereof”.

Lazendörfer et al. teach a method of treating psoriasis (column 3, lines 15-21) comprising administering a flavone (column 3, last paragraph, and columns 4-5) as in the limitation of claim 1, Step B. The flavones include genistein and luteolin (See column 3, last paragraph, and columns 4-5) of a flavone derivative comprising rutin as

in alpha-glucosylrutin as in the limitation of claim 16-17 (e.g., column 5, lines 30-67). Lazendorfer et al. teach administration, including topical and oral administration, including tablets (column 22, lines 21-40, 50-51). Oral administration reads upon the limitation “enterally” in instant claim 6. The limitation of claim 7: “administered parenterally" is taught, e.g., in column 22, lines 50-51.

It has been held that combinations of two or more compositions each of which is taught by the prior art to be useful for the same purpose in order to form a third composition which is to be used for the very same purpose. In re Susi, 58 CCPA 1074, 1079-80, 440 F.2d 442, 445, 169 USPQ 423, 426 (1971); In re Crockett, 47 CCPA 1018, 1020-21, 279 F.2d 274, 276-77, 126 USPQ 186, 188 (1960). As the court explained in Crockett, the idea of combining them flows logically from their having been individually taught in prior art. Therefore, since each of the reference teach that are effective in treating psoriasis, it would have been obvious to combine the two compounds with the expectation that such a combination would be effective in treating psoriasis. Thus, combining them flows logically from their having been individually taught in prior art. The adjustment of particular conventional working conditions (e.g., determining appropriate modes and protocols for the administration of the active agents within such method) is deemed merely a matter of judicious selection and routine optimization that is well within the purview of the skilled artisan. As such, it would have been obvious to one skilled in the art at the time of invention to determine all optimum and operable conditions (e.g., mode of administration, site of administration), because such conditions are art-recognized result-effective variables that are routinely

determined and optimized in the art through routine experimentation ("[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.". *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955). See MPEP 2145.05). One would have been motivated to determine all optimum and operable conditions in order to achieve the safest and most effective method in the most efficient manner. One would have had a reasonable expectation for success because such modifications are routinely determined and optimized in the art through routine experimentation.

From the teaching of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Claims 1 and 7-10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ledger (WO 96/01645) in view of Lazendörfer et al. (US 5,952,373) and Committee on Drugs (Pediatrics, 1997; cited in the IDS dated 01/10/06).

Ledger and Lazendörfer et al. are relied upon as above.

Neither reference expressly teaches the limitations of claims 8: "administered intranasally", of claim 9: "administered sublingually" and of claim 10: "administered by buccal administration".

Committee on Drugs teaches that during the past 20 years advances in drug formulations and innovative routes of administration have been made. The

urdderstanding of drug transport across tissues has increased. These changes have often resulted in improved patient adherence to the therapeutic regimen and pharmacologic response. The administration of drugs by transdermal or transmucosal routes offers the advantage of being relatively painless. Also, the potential for greater flexibility in a variety of clinical situations exists, often precluding the need to establish intravenous access, which is a particular benefit for children (e.g. abstract). Committee on Drugs teach that amongst transmucosal types of administration are nasal mucosal administration, which reads upon "intranasally" as in claim 8 (e.g., page 146, column 2); oral transmucosal comprising "sublingual" and "buccal" administration, as in claims 9-10 (e.g., page 147, columns 1-2).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the methods of Ledger and Lazendörfer et al. by using transmucosal routes of administration such as intranasal, sublingual and buccal. The skilled artisan would have been motivated to do so since Ledger teaches that these modes of administration are relatively painless, have the potential for greater flexibility in a variety of clinical situations and preclude the need to establish intravenous access which is a particular benefit for children (e.g., abstract, pages 146-147; Academy of Pediatrics). There would have been a reasonable expectation of success, given that both Ledger and Lazendörfer et al. teach various methods of administration as acceptable ways to introduce the compound in the patient. The adjustment of particular conventional working conditions (e.g., determining appropriate modes and sites for the administration of the active agents within such method) is deemed merely a matter of

judicious selection and routine optimization that is well within the purview of the skilled artisan. As such, it would have been obvious to one skilled in the art at the time of invention to determine all optimum and operable conditions (e.g., mode and/or site of administration), because such conditions are art-recognized result-effective variables that are routinely determined and optimized in the art through routine experimentation ("[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.". *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955). See MPEP 2145.05). One would have been motivated to determine all optimum and operable conditions in order to achieve the safest and most effective method in the most efficient manner. One would have had a reasonable expectation for success because such modifications are routinely determined and optimized in the art through routine experimentation.

From the teaching of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Conclusion

No claim is allowed.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MARCELA M. CORDERO GARCIA whose telephone number is (571)272-2939. The examiner can normally be reached on M-F 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia J. Tsang can be reached on (571) 272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Marcela M Cordero Garcia/
Patent Examiner, Art Unit 1654

MMCG 09/08